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(71) Applicant: AMGEN INC. [US/US]; One Amgen Center Drive, Thousand Oaks, CA 91320-1799 (US).

(72) Inventors: SANTORA, Vincent; 2623 Miller Place, Thousand Oaks, CA 91362 (US). ASKEW, Benny; 515 Havenside Avenue, Newbury Park, CA 91320 (US). GHOSE, Arup; 4023 Corte Cancion, Thousand Oaks, CA 91360 (US). HAGUE, Andrew; 488 Yorba Linda, Camarillo, CA 93012 (US). KIM, Tae, Seong; 1550 Dover Avenue, Thousand Oaks, CA 91360 (US). LABER, Ellen; 2589 Clearview Avenue, Ventura, CA 91362 (US). LI, Aiwen; Suite F, 587 North Ventu Park Road, P.O. Box 725, Newbury Park, CA 91320 (US). LIAN, Brian; 1322 Fenbrook Lane, Bloomington, IN 47401 (US). LIU, Gang; 491 Pesaro Street, Oak Park, CA 91377 (US). NORMAN, Mark, Henry; 130 Venus Street, Thousand Oaks, CA 91360 (US). SMITH, Leon; 33 Julie Court, Sommerset, NJ 08873 (US). TASKER, Andrew; 561 Granite Hills

Street, Simi Valley, CA 93065 (US). TEGLEY, Christopher; 478 Thunderhead Street, Thousand Oaks, CA 91360 (US). YANG, Kevin; 8871 Camino Real Avenue, San Gabriel, CA 91775 (US).

(74) Agents: ODRE, Steven, M. et al.; Amgen Inc., One Amgen Center Drive, M/S 27-4-A, Thousand Oaks, CA 91320-1799 (US).

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(54) Title: UREA COMPOUNDS AND METHODS OF USES

(57) Abstract: Selected novel urea compounds are effective for prophylaxis and treatment of diseases, such as cell proliferation or apoptosis mediated diseases. The invention encompasses novel compounds, analogs, prodrugs and pharmaceutically acceptable salts thereof, pharmaceutical compositions and methods for prophylaxis and treatment of diseases and other maladies or conditions involving stroke, cancer and the like. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.



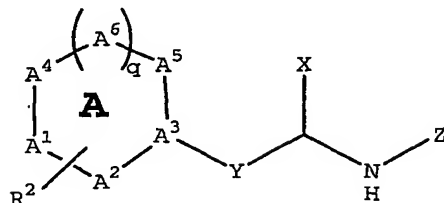
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WHAT IS CLAIMED IS:

1. A compound of formula I



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wherein each of A<sup>1</sup>-A<sup>6</sup> is selected from CH<sub>2</sub>, CH, C, O, S, NH and N; wherein A<sup>1</sup>-A<sup>6</sup> together form a ring A selected from

10 additionally substituted or unsubstituted 5- or 6-membered heterocyclyl,  
 additionally substituted or unsubstituted 5- or 6-membered heteroaryl fused with a phenyl group,  
 additionally substituted or unsubstituted 5- or 6-membered cycloalkenyl, and  
 15 additionally substituted or unsubstituted phenyl,  
 wherein the ring A is additionally substituted with one or more substituents independently selected from halo, -OR<sup>3</sup>, -SR<sup>3</sup>, -CO<sub>2</sub>R<sup>3</sup>, -CO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -COR<sup>3</sup>, -NR<sup>3</sup>R<sup>3</sup>, -SO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(O)OR<sup>3</sup>, -NR<sup>3</sup>C(O)R<sup>3</sup>,  
 20 cycloalkyl, optionally substituted phenylalkylenyl, optionally substituted 5-6 membered heterocyclyl, optionally substituted heteroarylalkylenyl, optionally substituted phenyl, lower alkyl, cyano, lower hydroxyalkyl,  
 25 nitro, lower alkenyl, lower alkynyl and lower haloalkyl;

wherein X and Z taken together form a nitrogen containing ring selected from

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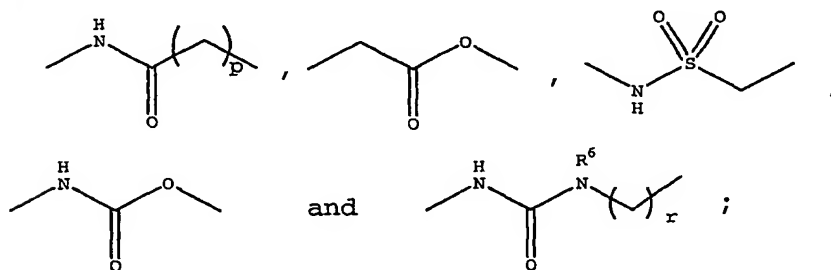
unsubstituted 5-6 membered heterocyclyl,  
 unsubstituted 5-6 membered heterocyclyl fused with a  
 phenyl group,

5-6 membered heterocyclyl substituted with one or  
 5 more substituents independently selected from  $R^1$ ,  
 and

5-6 membered nitrogen-containing heterocyclyl, fused  
 with a phenyl group, substituted with one or more  
 substituents independently selected from  $R^1$ ;

10 wherein  $R^1$  is independently selected from H, halo, -  
 $OR^3$ ,  $-SR^3$ ,  $-CO_2R^3$ ,  $-CO_2NR^3R^3$ ,  $-COR^3$ ,  $(-CONR^3R^3)$ ,  $-NR^3R^3$ ,  
 $-C(S)NR^3R^3$ ,  $-SO_2NR^3R^3$ ,  $-NR^3C(O)OR^3$ ,  $-NR^3C(O)R^3$ ,  
 cycloalkyl, optionally substituted phenylalkylenyl,  
 optionally substituted 4-10 membered heterocyclyl,  
 15 optionally substituted 4-10 membered  
 heterocyclylalkyl, optionally substituted phenyl,  
 optionally substituted phenoxy, lower alkyl, lower  
 cyano, lower alkenyl, lower alkynyl and lower  
 haloalkyl;

20 wherein Y is selected from, in either orientation,



wherein  $R^2$  is selected from  
 lower alkylaminoalkynyl,  
 25 cycloalkenyl- $C_{2-3}$ -alkynyl,  
 cycloalkyl- $C_{2-3}$ -alkynyl,  
 phenyl- $C_{2-3}$ -alkynyl,

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5-6 membered heterocyclyl-C<sub>2-3</sub>-alkynyl,  
substituted or unsubstituted cycloalkenyl,  
substituted or unsubstituted phenyl,  
substituted or unsubstituted 5-6 membered  
5 heterocyclyl, and  
substituted or unsubstituted 5-6 membered  
heterocyclyl bridged with a phenyl group;  
wherein substituted R<sup>2</sup> is substituted with one or  
more substituents independently selected from  
10 halo, -OR<sup>3</sup>, -SR<sup>3</sup>, -CO<sub>2</sub>R<sup>3</sup>, -CO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -COR<sup>3</sup>, -  
NR<sup>3</sup>R<sup>3</sup>, -C(O)NR<sup>3</sup>R<sup>3</sup>, -SO<sub>2</sub>NR<sup>3</sup>R<sup>3</sup>, -NR<sup>3</sup>C(O)OR<sup>3</sup>, -  
NHC(O)R<sup>3</sup>, -SO<sub>2</sub>NHC(O)R<sup>3</sup>, -C(S)NR<sup>3</sup>R<sup>3</sup>, nitro,  
cycloalkyl, optionally substituted  
phenylalkylenyl, optionally substituted 4-7  
15 membered heterocyclyl, optionally substituted  
heterocyclylalkylenyl, optionally substituted  
phenyl, optionally substituted  
phenoxyalkylenyl, optionally substituted  
heterocycliloxyalkyl, lower alkyl, cyano, lower  
20 hydroxyalkyl, lower alkoxyalkyl, lower  
azidoalkyl, lower aminoalkyl, lower  
(hydroxyalkyl)aminoalkyl, lower  
alkylaminoalkyl, lower alkylaminoalkoxy, lower  
aminoalkoxyalkyl, lower (alkylaminoalkyl)amino  
25 lower ((alkylamino)alkylamino)alkyl, lower  
alkylaminoalkylaminocarbonyl, lower cyanoalkyl,  
lower alkenyl, lower alkynyl and lower  
haloalkyl;  
wherein R<sup>3</sup> is selected from H, lower alkyl, optionally  
30 substituted phenyl, optionally substituted  
phenylalkyl, optionally substituted heterocyclyl,

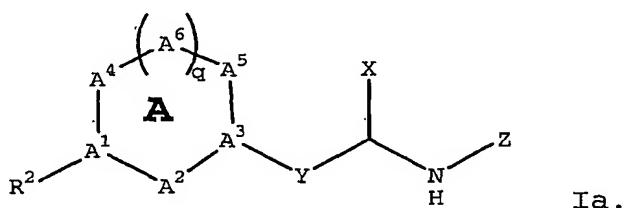
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optionally substituted heterocyclalkyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, and lower haloalkyl;  
wherein R<sup>6</sup> is selected from H, alkyl, 5-6 membered heterocyclalkylenyl and alkylamino;  
5 wherein p is 1 or 2;  
wherein q is 0 or 1; and  
wherein r is 0-3;  
and pharmaceutically acceptable salts thereof;  
provided A is not thiazol-2-yl when Y is ureido;  
10 further provided A is not phenyl when R<sup>2</sup> is pyridyl or pyrimidyl when Y is ureido and when X and Z taken together form 1-methylindolyl; further provided A is not 1-phenylpyrazol-4-yl when Y is ureido when X and Z taken together form pyrazolyl and when R<sup>2</sup> is  
15 pyrrol-1-yl; further provided A is not 5-methylpyrazol-3-yl when Y is ureido when X and Z taken together form pyrazolyl and when R<sup>2</sup> is phenyl; further provided A is not thiazolyl or dihydrothiazolyl when R<sup>2</sup> is indolyl when Y is ureido  
20 and when X and Z taken together form thiazolyl or dihydrothiazolyl; further provided A is not pyrazolyl or dihydropyrazolyl when R<sup>2</sup> is 2-furyl when Y is ureido and when X and Z taken together form thiazolyl or dihydrothiazolyl when R<sup>1</sup> is  
25 isopropyl; further provided A is not oxadiazolyl or dihydrooxadiazolyl when R<sup>2</sup> is phenyl when Y is ureido and when X and Z taken together form thiazolyl or dihydrothiazolyl when R<sup>1</sup> is isopropyl; provided A is not thiazolyl when R<sup>2</sup> is 3-pyridyl  
30 when Y is ureido and when X and Z taken together form 2-(3-pyridyl)thiazol-4-yl; and further provided

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A is not thien-3-yl when Y is ureido when X and Z taken together form thienyl and when R<sup>2</sup> is pyrrol-1-yl.

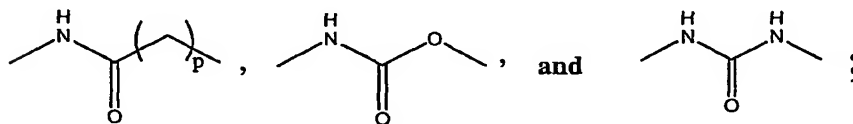
- 5            2. Compound of Claim 1 and pharmaceutically acceptable salts thereof, of formula Ia



- 10            3. Compound of Claim 2, and pharmaceutically acceptable salts thereof, wherein A is selected from 5- or 6- membered heterocyclyl.

4. Compound of Claim 3, and pharmaceutically  
15 acceptable salts thereof, wherein A is selected from 5- or 6- membered heteroaryl.

5. Compound of Claim 4, and pharmaceutically acceptable salts thereof, wherein A is selected from  
20 thiazolyl, oxazolyl, imidazolyl, pyrrolyl, pyrazolyl, isoxazolyl, triazolyl and isothiazolyl; wherein Y, in either orientation is selected from



- 25            wherein p is 1-2;